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# Amebic encephalitis caused by *Balamuthia mandrillaris*: report of four cases

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**We report four fatal cases of amebic encephalitis in children caused by the free-living pathogenic ameba *Balamuthia mandrillaris.* The clinical course ranged from subacute to fulminant. Provisional diagnoses were made either shortly before death or postmortem by an indirect immunofluorescent antibody test. Although the four cases occurred in different geographic locations, their common features may have diagnostic value for recognizing future cases of amebic encephalitis. The cases occurred in children 2 to 7.5 years old who were ostensibly immunocompetent and of Hispanic ethnicity. Three of the four children developed hydrocephalus during their illness. Increased awareness and timely diagnosis of this disease entity might lead to earlier intervention with improved outcome.**

The free-living amebas *Naegleria* and *Acanthamoeba* are recognized as causal agents of meningoencephalitis and granulomatous encephalitis, respectively.[1] More recently a third free-living ameba, *Balamuthia mandrillaris*, was identified as the causal agent of granulomatous encephalitis in humans and other animals. Initial reports of the disease in humans suggested that immunosuppression or immunodeficiency was an important risk factor in determining susceptibility,[2, 3] but the disease has also occurred in immunocompetent children and adults.[4–6] Most cases of *Balamuthi*a encephalitis are diagnosed postmortem, based on finding amebas in brain sections with hematoxylin-eosin or immunofluorescence staining.

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We report four cases of *Balamuthia* encephalitis in immunocompetent children, ages 2 to 7.5 years. The use of an indirect immunofluorescence technique enabled premortem diagnoses in three of the four cases at the California Encephalitis Project. Despite the premortem diagnoses the insidious progression of the disease and the lack of optimal amebacidal therapy resulted in fatal outcomes in all cases. Common features among the four individuals that might be of value in recognition of future cases of *Balamuthia* encephalitis were high protein values in cerebrospinal fluid, hydrocephalus and Hispanic ethnicity.

## CASE PRESENTATIONS

**Case 1 (Sonoma County, CA).** A 3-year-old Caucasian-Hispanic girl was admitted to the intensive care unit in a coma. She had a 10-day history of fever, fatigue and emesis and two generalized tonic-clonic seizures. Her past medical history was unremarkable, except for an episode of acute otitis media ~1 month before onset which was treated with a 10-day course of amoxicillin. There was a history of household exposure to a cat, parakeet and cockatiel and a fresh-water aquarium with fish. There was no history of camping or swimming. There was no known exposure to tuberculosis, but there was exposure to a close family friend with chronic cough.

Physical examination was significant for an intubated, ventilated child, who was febrile. She was comatose and had pinpoint pupils, which were nonreactive to light, absent gag and corneal reflexes, no response to sternal rub, withdrawal of extremities in response to painful stimuli of hands or feet and hyperactive and symmetric deep tendon reflexes.

Peripheral white blood cell count was 8700/mm$^3$ with 63% segmented neutrophils, 7% band forms, 16% lymphocytes, 13% monocytes and 1% eosinophils. Hemoglobin was 10.8 g/dl. Platelet count was 340 000/mm$^3$. Serum electrolytes, blood urea nitrogen, creatinine, liver function tests, total protein, albumin, ammonia, coagulation studies and urinalysis were normal.

Magnetic resonance imaging (MRI) scan of the head showed marked ventriculomegaly with a patent fourth ventricle suggesting communicating hydrocephalus and a few areas of focal increased signal within the

right posterior frontal and temporal cerebral cortex. The placement of an external ventricular drain did not lead to improvement in neurologic status. Cerebrospinal fluid (CSF) obtained by lumbar puncture showed a leukocyte count of 354 cells/mm$^3$ with 46% neutrophils, 48% lymphocytes, 5% monocytes and 1% basophils; protein was 1247 mg/dl and glucose was 6 mg/dl.

Multiple stains and cultures for acid-fast bacilli from CSF and tracheal aspirate secretions were negative. PCR for *Mycobacterium tuberculosis* on spinal fluid was also negative. Skin tests with purified protein derivative and *Candida* antigen showed no induration and ~5 mm induration, respectively. There were no areas of infiltrate or atelectasis on the initial chest roentgenogram. Active tuberculosis was ruled out in all household contacts and close family friends.

Multiple bacterial and fungal cultures from blood and CSF were negative. Serologic tests for *Toxoplasma gondii*, *Coccidioides immitis*, *Mycoplasma pneumoniae*, *Bartonella henselae, Bartonella quintana* and HIV were negative. Antigen testing for *Cryptococcus neoformans* on blood and CSF was negative. PCR for human herpes simplex virus on CSF was negative. Ophthalmologic examination revealed normal fundi and cornea.

The patient was empirically treated for tuberculous meningitis with isoniazid, rifampin, ethambutol, pyrazinamide and methylprednisolone, as well as ceftriaxone and acyclovir.

On Day 24 of her illness an electroencephalogram documented electrocerebral silence consistent with the clinical diagnosis of brain death. Supportive care was withdrawn. On the day before her death, cells with ameboid morphology consistent with *Balamuthia* were identified on wet mount of the CSF. Serum obtained 5 days before the patient's death had a *B. mandrillaris* titer of 1/512. At autopsy the brain had massive necrosis of gray and white matter and amebic trophozoites, particularly around the fourth ventricle and brain stem. The amebas were clustered around vessels. The meninges were thickened. Amebas were not found in other organs. Immunofluorescence on brain tissue sections confirmed the presence of *B. mandrillaris* (Figs. 1 and 2), and the organism subsequently grew on cultures of monkey kidney cells inoculated with macerated fragments of the patient's brain tissue.

**Case 2 (Riverside County, CA).** A 2-year-old Hispanic girl was admitted with facial palsy and hemiparesis. Three weeks before admission the patient had a low grade fever and headache, was diagnosed with otitis media and was treated with oral antibiotics. Two weeks before admission the mother noted lateral deviation of the child's left eye. An ophthalmologist diagnosed papilledema. Computed tomographic (CT) scan of her head was normal. Several days later the patient awoke with a right-sided hemiparesis. Her exposure history was significant for frequent contact with a grandmother who had a chronic cough, and the child had traveled to Mexico 2 months before onset of illness.

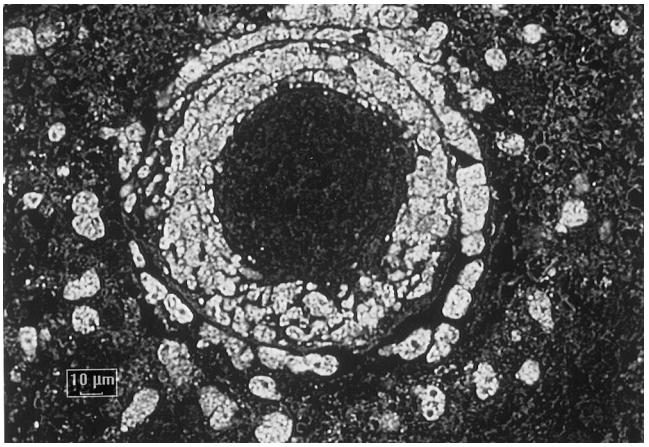


FIG. 1. Section of brain stem from Case 1, stained by immunofluorescence showing multiple *Balamuthia* trophozoites. Amebas are seen tightly packed in the perivascular region of a blood vessel and scattered individually in the matrix. The perivascular location of the amebas is typical in *Naegleria, Acanthamoeba* and *Balamuthia* encephalitides. Original magnification, ×500.

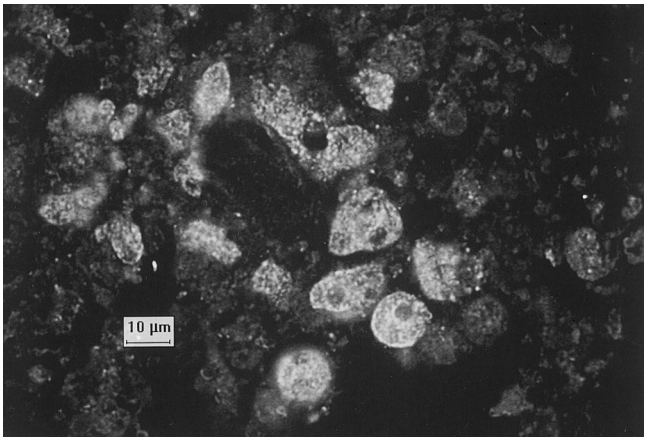


FIG. 2. Section of brain tissue from Case 1, stained by immunofluorescence, showing multiple trophic *Balamuthia* amebas surrounding the lumen of a blood vessel. Nuclei can be seen in several of the amebas as a clear, unstained vesicle. Original magnification, ×900.

On admission the patient was afebrile and lethargic, with normal vital signs. She complained of headache. Neurologic examination was significant for right esotropia, right ptosis with a right facial palsy, a right Babinski sign and a mild (Grade 1/5) right hemiparesis.

Laboratory examination revealed a white blood cell count of 6500/mm$^3$ with 35% segmented neutrophils, 50% lymphocytes, 10% monocytes, 3% eosinophils and 2% basophils; hemoglobin was 11.7g/dl, and platelet count was 297 000/mm$^3$. CSF revealed a leukocyte count of 124/mm$^3$ with 1% segmented neutrophils, 13% monocytes, 72% lymphocytes and 14% eosinophils. Pro-

tein and glucose concentrations were 84 and 58 mg/dl, respectively. Gram stain, fungal stain and acid-fast stain on CSF were negative. MRI of her head revealed multiple enhancing lesions in the brain stem. An electroencephalogram showed diffuse cerebral dysfunction.

The patient was treated empirically for tuberculous meningitis with isoniazid, rifampin, pyrazinamide, ethambutol and fluconazole, as well as with dexamethasone and ceftriaxone. During the ensuing 24 h, the patient's mental status deteriorated, and she required intubation because of decreased respiratory effort. Repeat CT scan of the brain showed hydrocephalus. The patient was taken to the operating room, where an external ventricular drain was placed and a brain biopsy was obtained. The biopsy revealed chronic inflammation with no obvious infectious agent or malignancy. Despite maximum supportive care the patient died the following day.

Autopsy of the brain demonstrated hemorrhagic meningitis with multiple cerebral, cerebellar and brain stem infarctions. There were numerous amebic trophozoites in the meninges and brain tissue. Immunofluorescence performed on brain sections identified the organism as *B. mandrillaris*. Examination of other organs at autopsy revealed the presence of trophozoites only in the lungs.

**Case 3 (Orange County, CA).** A 7-year-old Hispanic boy was admitted for new onset of focal seizures, development of wide based gait and right cranial nerve VI palsy. Complete blood count and chemistry panel were normal. A CT scan of the head showed a 1-cm-enhancing lesion on the right frontal cortex. MRI showed multiple subcortical enhancing lesions in the left dorsal aspect of the pons and the right cerebellar hemisphere consistent with neurocysticercosis, and the patient was treated with dexamethasone and albendazole. Initial cysticercosis titers on serum were negative.

The patient was discharged home to receive albendazole. During the following month the patient was hospitalized twice for fever, chills and abdominal pain. Repeat cysticercosis serum titers were obtained and returned positive. A second MRI showed increased edema with mass effect surrounding the right dorsal pons and two new punctate lesions in the left parietal gray/white matter and left paraventricular deep white matter in the parietal occipital junction, again suggestive of neurocysticercosis. Treatment with dexamethasone and albendazole was continued.

Approximately 1 month after the initial hospitalization, the patient was hospitalized for a fourth time with an acute febrile illness, with temperature to 39°C mostly noted in the evenings. His mother had also noted a change in his personality with increased temper tantrums and more aggressive behavior. A third MRI showed multiple new lesions. Peripheral white blood cell count was 8200/mm$^3$, with a normal differential. Hemoglobin was 12.4 g/dl. Platelet count was 279 000/mm$^3$. A lumbar puncture showed a leukocyte count of 230/mm$^3$, red blood cell count of 3/mm$^3$, protein 308 mg/dl and glucose <20 mg/dl. Repeat CSF evaluations showed consistently elevated CSF protein and pleocytosis.

Serologic tests for HIV, *T. gondii* and *Bartonella henselae* were negative. The following CSF studies were negative: PCR for HSV type 1 and 2; PCR for *M. tuberculosis*, antibodies for *Coccidioides immitis*, *Taenia solium* and *Cryptococcus neoformans*.

The patient was empirically treated with isoniazid, rifampin, pyrazinamide, ethambutol, meropenem and amphotericin B. The patient's mental status continued to deteriorate, and he became progressively more lethargic. A brain biopsy showed necrotizing granulomatous tissue consistent with an amebic infection. Flucytosine was added to the treatment regimen. The patient's serum titers for *B. mandrillaris* were elevated at 1/512. After a prolonged course in the intensive care unit, a brain flow study demonstrated brain death. The patient was discontinued from life support and died on Day 45 of illness.

**Case 4 (Bexar County, TX).** A 30-month-old Hispanic boy had a 2.5-week history of intermittent fever and emesis. He developed ataxia and was evaluated with a CT scan and MRI of the head. The scans demonstrated four discrete lesions in the brain. Peripheral white blood cell count was 6500/mm$^3$, hemoglobin was 10 g/dl and platelet count was 345 000/mm$^3$. CSF analysis showed a leukocyte count of 14/mm$^3$ with 100% lymphocytes, protein 116 mg/dl and glucose 39 mg/dl. A brain biopsy revealed a granulomatous process, with negative acid-fast bacillus and fungal stains. Amebas were seen on histopathologic analysis, and a direct fluorescent antigen was positive for ameba. Immunologic studies were normal (flow cytometry, complete blood count with differential, immunoglobulins, HIV and total hemolytic complement).

Treatment was initiated with intravenous pentamidine, metronidazole, fluconazole, amphotericin B and oral itraconazole, flucytosine, azithromycin and sulfadiazine. Granulocyte colony-stimulating factor and thorazine were added later. With clinical deterioration, homeopathic medications were started at the family's request (Wild Bear's Garlic, Vermex, Concentrated Grape Fruit, Amoebatox, Lymphoplex). An extraventricular catheter was placed for hydrocephalus.

Titers for *B. mandrillaris* on the serum and spinal fluid were positive with values of 1/256 to 1/512 and 1/32, respectively. Sections of brain tissue stained with anti-*Balamuthia* serum revealed amebas. Laboratory evaluation for *Acanthamoeba* was negative.

The patient tolerated the regimen of medications without difficulty, but his disease continued to progress with seizures and severe encephalopathy requiring intubation/tracheostomy and gastrostomy tube. CSF on Day 40 of therapy showed a leukocyte count of

83/mm$^3$, protein of 1600 mg/dl and glucose of 47 mg/dl. He was declared brain dead and died on Day 60 of therapy.

## DISCUSSION

*B. mandrillaris* is a free-living ameba, which causes meningoencephalitis in immunocompetent and immunocompromised humans and animals.[1] Amebic encephalitis is classically divided in two clinical entities: (1) primary amebic meningoencephalitis, which is usually caused by *Naegleria fowleri*; and (2) granulomatous amebic encephalitis, caused by *Acanthamoeba* spp. or *Balamuthia* and occurring in chronically ill or immunosuppressed patients.

The onset of granulomatous amebic encephalitis is insidious, and initial symptoms may include fever, headache, stiff neck, cranial nerve palsies (third and sixth cranial nerves), ataxia, hemiparesis, seizures and personality change. The clinical course is subacute to chronic and often leads to death within weeks to several months, even as long as 2 years.[7–9] Some children developing *Balamuthia* encephalitis had facial lesions and/or rhinitis with infections of the sinus cavities.[4, 9]

The first documented CNS infection caused by *B. mandrillaris* occurred in a pregnant mandrill baboon that died of encephalitis at the San Diego Wildlife Park in 1990.[2, 10] The following year *Balamuthia* granulomatous encephalitis was described in a patient with AIDS.[3] Cases such as those reported in this paper have occurred in immunocompetent children [4–6, 11] Several cases of granulomatous amebic encephalitis attributed to *Acanthamoeba* were retrospectively identified as *B. mandrillaris* cases.[5, 12–14] At present ~80 published cases of *B. mandrillaris* infection in humans and animals have been reported globally, with about one-half of these in the United States (GS Visvesvara, Atlanta, GA, personal communication). Suggested portals of entry are lungs, skin and sinus cavities, followed by hematogenous spread to tissues including the central nervous system. The presence of the ameba in either its trophic or cystic stages in soil has been conjectured as a source of infection in several cases, either through the respiratory tract or through breaks in the skin. Case reports of patients with multiple foci of infection suggest hematogenous dissemination.

Most patients with *B. mandrillaris* meningoencephalitis present with focal neurologic findings and seizures.[4, 6, 12–15] There is no particular age predilection. Some of the patients are febrile at the time of presentation.[3, 5, 12–14, 16] Peripheral complete blood counts are usually normal.[5, 12, 13] In most cases CSF findings are significant for pleocytosis up to 500 white blood cells/mm$^3$ with lymphocytic and monocytic predominance. CSF protein is usually mildly to moderately elevated, but can be highly elevated (1 to 2 g/dl), and glucose concentrations can be normal or decreased.[5, 15, 17] Radiographic imaging may show focal enhancing lesions, cystic lesions, diffuse brain edema, hydrocephalus and lesions compatible with stroke.[3, 5, 12–16] Biopsy or autopsy specimens show hemorrhagic necrosis of the brain with amebic trophozoites and cysts and inflammatory infiltrate with lymphocytes and monocytes. There are clusters of amebas and inflammatory cells in the perivascular spaces around blood vessels (Figs. 1 and 2). True granulomas have not been described.[2, 3, 5, 12–16] Motile cells with an ameboid morphology were seen on a wet mount of spinal fluid in Case 1. Although amebas were cultured from brain tissue in Case 1, attempts to culture them from spinal fluid in Cases 1 and 4 were unsuccessful. Fresh tissue suitable for isolation of amebas was not available from the other cases.

Several features were common to the four cases described in this report (Table 1). All four patients were of Hispanic ethnicity. Of specimens from the United States submitted to the Centers for Disease Control for *Balamuthia* testing, ~44% of the positives were from individuals of Hispanic ethnicity (GS Visvesvara, Atlanta, GA, personal communication), whereas 12% of the US population is Hispanic (US Census Bureau statistics for the year 2000). The reasons for the apparent higher numbers of *Balamuthia* encephalitis cases among Hispanics may be a predisposing genetic factor or occupational or environmental circumstances. Other features in common were a history of otitis media (two of four cases), hydrocephalus that developed later in the course of the disease (three of four cases) and unusually high levels of protein (>1000 mg/dl) in the CSF (three of four cases). Otitis media occurred in several cases reported in the literature,[13, 14, 16, 17] and hydrocephalus has been reported in other cases.[5, 16]

Typically diagnosis of *Balamuthia* encephalitis is made on postmortem examination of brain tissue. There are two known survivors of confirmed *Balamuthia* encephalitis. One, a California resident in his 60s, survived with severe neurologic deficits after treatment with fluconazole, sulfadiazine, clarithromycin and flucytosine. The second case, that of a Mexican-American child residing in California, recovered after treatment with a similar combination of antimicrobials (TR Deetz, MH Sawyer, G Billman, FL Schuster, GS Visvesvara. Successful treatment of *Balamuthia* amebic encephalitis: presentation of two cases. Submitted for publication).[11]

Neurocysticerosis was suspected in Case 3. Cysticercosis was suspected in other *Balamuthia* cases,[18, 19] as well as in a case of encephalitis initially reported as caused by *Acanthamoeba*[20] but subsequently found to have been caused by *Balamuthia* (GS Visvesvara, Atlanta, GA, unpublished observation). Serology in such cases may be positive, suggesting cross-reactivity with *Balamuthia* or other unrelated exposure. Previous reports of *Balamuthia* cases have included tumors, cysticercosis and tuberculoma or tuberculous meningitis as presumptive diagnoses.[5] Tubercular meningitis was

**TABLE 1.** Comparative features of the four *Balamuthia* encephalitis cases

| Demographics | Prodrome | Presentation on Admission | Lumbar Puncture Results | CNS Imaging | Differential Diagnosis and/or Treatment | Duration of Illness and Outcome |
|---|---|---|---|---|---|---|
| Case 1: 3-yr-old Hispanic girl; Sonoma Co., CA | 10-day history of fever, fatigue, otitis media | Fever, emesis, dehydration, tonic-clonic seizures | LP on HD 2 WBC 540/$mm^3$ (90N/10L)<br>Prot 122 mg/dl<br>Gluc 47 mg/dl<br>LP on HD 19<br>WBC 105/$mm^3$ (79L/15N/6M)<br>Prot 1918 mg/dl<br>Gluc 4 mg/dl | Hydrocephalus; right frontal (1 cm) and temporal lobe (0.5 cm) lesions (MRI) | Empirical treatment for MTb | 4 wks; died HD 25 |
| Case 2: 2-yr-old Hispanic girl; Riverside Co., CA | ~3-wk history of fever, headache, otitis media, lateral deviation of left eye | Afebrile, headache, right facial palsy and hemiparesis, lethargy | LP on HD 1<br>WBC 124/$mm^3$ (72L/13M/1N)<br>Prot 84 mg/dl<br>Gluc 58 mg/dl | Hydrocephalus; enhancing lesions in posterior capsule (3 by 2 cm) and left frontal subcortical region (1.5 cm) (MRI) | Empirical treatment for MTb | 3–4 wk; died HD 3 |
| Case 3: 7-yr-old Hispanic boy; Orange Co., CA | ~3-wk history of fever, chills, abdominal pain | Fever, focal seizures, wide based gait, right cranial nerve (VI) palsy, personality change | LP on HD 2<br>WBC 230/$mm^3$ (62L/12N/4M)<br>Prot 308 mg/dl<br>Gluc <20 mg/dl<br>LP on HD 26<br>WBC 102/$mm^3$ (91L/2M/1N)<br>Prot 1400 mg/dl<br>Gluc 62 mg/dl | Enhancing 1-cm lesion in right frontal cortex (CT); subcortical lesions in pons and cerebellum (MRI); increased edema | Empirical treatment for neurocysticercosis, MTb | 6 wk; died HD 47 |
| Case 4: 2.5-yr-old Hispanic boy; Bexar Co., TX | 2.5-wk history of emesis and fever | Emesis, ataxia | LP on HD 1<br>WBC 14/$mm^3$ (100%L)<br>Prot 116 mg/dl<br>Gluc 39 mg/dl<br>LP on HD 40<br>WBC 83/$mm^3$<br>Prot 1600 mg/dl<br>Gluc 47 mg/dl | Hydrocephalus; 4 discrete 1–2-cm lesions (MRI) | Early empirical treatment for MTb; empirical treatment for *Acanthamoeba* granulomatous encephalitis (based on brain biopsy) | 14 wk; died HD 62 |

CNS, central nervous system; LP, lumbar puncture; HD, hospital day; WBC, white blood cells; N, neutrophils; L, lymphocytes; M, macrophages; E, eosinophils; MTb, mycobacterial tuberculosis; Prot, protein; Gluc, glucose.

suspected in Cases 1, 2 and 4, as well as in other cases reported in the literature.[3, 5, 9, 12–14, 21, 22]

The common features seen in these four cases in conjunction with immunofluorescent testing may be of diagnostic value in detecting cases of amebic encephalitis in patients with encephalitis.

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